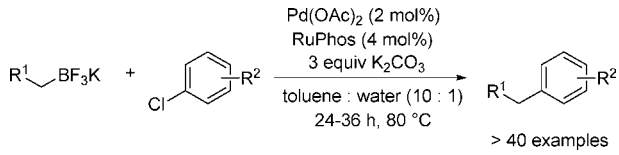
Organic Process Research & Development **2009,** *13,* 824–828

Highlights from the Literature

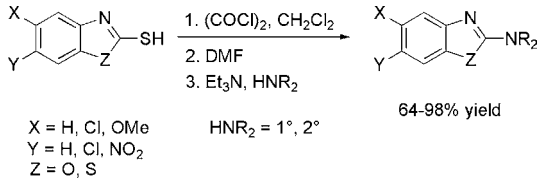
Some Items of Interest to Process R&D Chemists and Engineers

Cross-Coupling of Primary Alkyltrifluoroborates and Aryl Chlorides



A collaborative effort between the Molander group and Dreher at Merck has resulted in the development of general conditions for the Suzuki−Miyaura cross-coupling of primary alkyltrifluoroborates with aryl chlorides (*J. Org. Chem.* **2009**, *74*, 3626−3631). Specifically, parallel microscale techniques were used to rapidly explore the experimental space with maximum efficiency. Optimal conditions employ $Pd(OAc)_2$ (2 mol %) and Ru-Phos (4 mol %) as the catalyst precursors, 1 equiv of the requisite RBF_3K reagent and 3 equiv of K_2CO_3 as the base in a mixed solvent system composed of toluene/water (10:1). These conditions were found to be amenable to coupling with aryl bromides, iodides, and triflates as well. An important finding from this study is that the conditions developed previously for the cross-coupling of secondary alkyltrifluoroborates are not optimal for primary alkyltrifluoroborates. The authors note that this finding serves to demonstrate the value of parallel experimentation to develop novel, substrate-specific results.

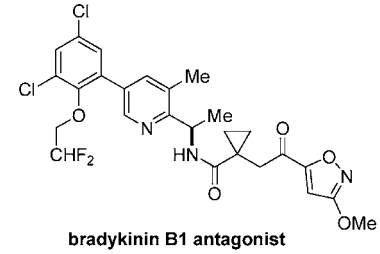
A One-Pot Synthesis of 2-Aminated Benzoxazoles and Benzothiazoles

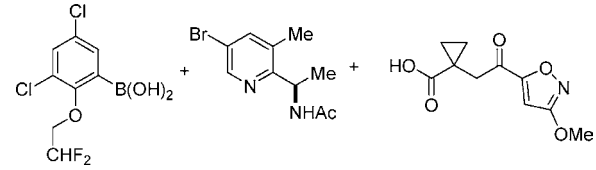


A method for the synthesis of 2-aminobenzoxazoles and 2-aminobenzothiazoles is reported by Stewart and co-workers at Merck (*J. Org. Chem.* **2009**, *74*, 3229−3231). Previous syntheses of 2-aminated benzoxazoles have relied on forcing thermal conditions to generate the products directly from the corresponding thiols. The resulting yields have ranged from moderate to poor. The current work describes an alternative mild and high-yielding one-pot chlorination−amination sequence. Compounds with a variety of substitution patterns are reported, and the method was successfully extended to benzothiazoles. Pd-catalysis (amination and Suzuki−Miyaura coupling) on suitably activated examples was also employed to further elaborate the initial products into substituted derivatives.

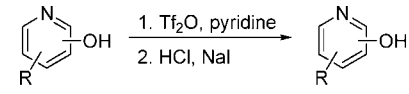
Practical Synthesis of a Potent Bradykinin B1 Antagonist

A practical synthesis of bradykinin B1 antagonist **1** is described by O'Shea and co-workers at Merck (*J. Org. Chem.* **2009**, *74*, 4574−4553). A convergent strategy was utilized, involving independent synthesis of three fragments followed by Suzuki−Miyaura biaryl synthesis and final amide bond formation. Key steps in the preparation of the pyridine fragment include the introduction of the fluorine atom via *ipso*-displacement of a nitro group and controlled generation of the benzylic amine-bearing stereocenter using enantioselective hydrogenation of an enamide precursor. The overall synthesis comprises 19 steps in total and delivers the target API in 35% yield from the commercially available pyridine raw material.





One-Pot Iodination of Hydroxypyridines

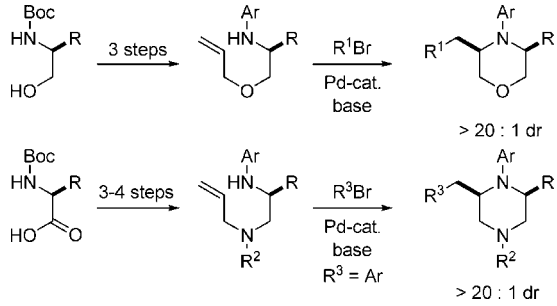


A high-yielding, one-pot iodination of hydroxypyridines and hydroxyquinolines is described by Maloney and co-workers at Merck (*J. Org. Chem.* **2009**, *74*, 5111−5114). The iodination proceeds under mild conditions, and the products are obtained in high yield without the need for chromatographic purification. In addition, this iodination procedure works on both 2- and 4-hydroxypyridines and hydroxyquinolines. Bromination is also possible when NaBr is substituted for NaI.

New Strategy for the Synthesis of Substituted Morpholines and Piperazines

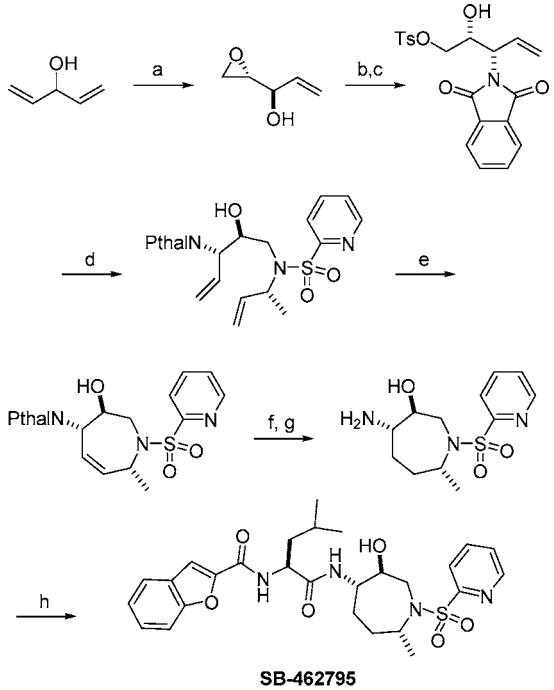
A four-step synthesis of *cis*-3,5-disubstituted morpholines from enantiomerically pure amino alcohols is described by the Wolfe group (*J. Org. Chem* . **2009**, *74*, 5107−5110). The key step in this approach is a Pd-catalyzed carboamination reaction between a substituted enantio-enriched ethanolamine derivative and an aryl or alkenyl bromide. The morpholine products are generated

Published on Web 08/31/2009
10.1021/op900215m CCC: $40.75



as single stereoisomers in moderate to good yield. This strategy also provides access to fused bicyclic morpholines as well as 2,3- and 2,5-disubstituted products. In a separate report from the same group, a similar strategy is applied to the synthesis of *cis*-2,6-disubstituted piperazines from amino acid precursors (*Tetrahedron* **2009**, *65*, 6549−6570). The target compounds are generated in 95−99% ee with good to excellent levels of diastereoselectivity (usually >20:1) using Pd-catalyzed carboamination reactions between aryl or alkenyl halides and substituted ethylenediamine derivatives to form the heterocyclic rings. The synthesis allows for the modular construction of piperazines bearing different substituents at N1, N4, C2, and C6. The use of this strategy for the construction of 2,3-disubstituted piperazines, fused bicyclic piperazines, and tetrahydroquinoxalines is also reported. In addition, the mechanism of the key carboamination reactions is discussed, and new models that predict and explain the stereochemical outcome of these transformations are presented.

Large-Scale Synthesis of SB-462795, a Cathepsin K Inhibitor

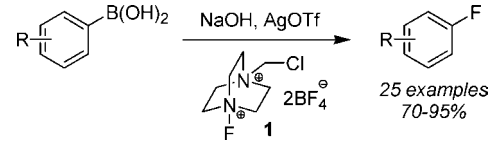


SB-462795

(a) Ti(Oi-Pr)4, 10 mol %, (-)-DIPT 13 mol %, CH_2Cl_2, cumene hydroperoxide1.1 equiv, 90%, 98% ee; (b) DIAD, 1.3 equiv, PPh_3, 1.3 equiv, tol, 85%; (c) p-TsOH, 1.1 equiv, Et_4NOTs, 1.05 equiv; (d) sulfonamide, BTPP 10 mol %,isopropanol, 73%; (e) 34 (0.5 mol %), toluene, 96%, residual Ru 359 ppm; (f) NH_2OH,MeOH, 73%; (g) 10% Pd/C, H_2, 98%; (h) carboxylic acid, EDC

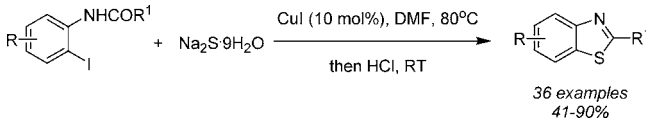
Wang and co-workers at GlaxoSmithKline (GSK) report on process development of SB-462795, a potent cathepsin K inhibitor (*Tetrahedron* **2009**, *65*, 6291−6303). A strategic element common to all the synthetic routes discussed is the RCM reaction used to construct the 7-membered azepanone ring. The evolution of various tactical iterations is described in detail. In an early route, an aldol−Curtius−RCM sequence was used to construct the key azepane moiety, and the stereochemistry at C4 was undefined until late in the synthesis. The main features of this route are: (1) an auxiliary-based aldol reaction involving a crotonate imide, (2) hydrazine-mediated auxiliary cleavage followed by a Curtius reaction to convert the resultant β,γ-unsaturated carbonyl intermediate into an allylamine derivative, and (3) an RCM reaction to generate the azepanone. Although the desired stereochemistry at C4 is readily controlled under thermodynamic equilibration conditions, the authors noted significant isolation problems associated with the processing of mixtures of stereoisomers. Consequently, second-generation routes sought to control the C4 stereocenter from the outset. In the final iteration (shown here), a Sharpless epoxidation−Mitsunobu sequence is used to establish the C3/C4 stereocenters, and other main features include: (1) a selective epoxide opening using TsOH to give the monotosylate of a vicinal diol, (2) an efficient epoxide opening reaction by a sulfonamide catalyzed by BTPP, and (3) an efficient RCM reaction. The final route is amenable to large-scale manufacturing, as demonstrated by the synthesis of over 200 kg of SB-462795.

Fluorination of Boronic Acids Mediated by Silver(I) Triflate



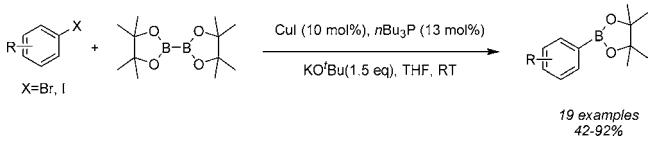
A new, general method for the fluorination of aryl- and alkenylboronic acids and esters mediated by AgOTf has been disclosed by Furuya and Ritter at Harvard University (*Org. Lett.* **2009**, *11*, 2860−2863). The reaction proceeds via transmetalation of the boronic acid to an isolable aryl silver complex in the presence of silver triflate and sodium hydroxide in methanol, followed by fluorination with commercially available 1-chloromethyl 1,4-diazoniabicyclo[2.2.2]octane tetrafluoroborate (F-TEDA-BF_4, **1**) in acetone. A variety of arylboronic acids participate in the reaction including electron-rich and electron-poor substituents. Arenes bearing protic, electrophilic and nucleophilic substitutions are also suitable substrates. This reaction can also be used to prepare alkenylboronic acids with retention of stereochemistry. Arylboronic esters such as pinacolates also participate, which allows for the powerful extension of one-pot hydrofluorination of alkynes via a hydroboration/fluorination sequence. The byproducts including F-TEDA-BF_4, TEDA-BF_4, and silver salts can be removed by a simple aqueous workup. Drawbacks to the system include the necessary solvent swap for the transmetalation step (methanol) and the fluorination step (acetone) and the deteterious actions of water in the reaction, which promotes formations of phenol byproducts.

Efficient and Economical Access to Substituted Benzothiazoles



A copper-catalyzed coupling of 2-haloanilides with metal sulfides and subsequent condensation to provide substituted benzothiazoles has been reported by Ma and co-workers at the Chinese academy of Sciences in Shanghai (*Angew. Chem., Int. Ed.* **2009**, *48*, 4222−4225). Under the optimized conditions, multiple functional groups could be introduced at the 2-position of the benzothiazoles including alkyl groups, protons, substituted aryl groups, and heterocycles. Both 2,5- and 2,6-disubstituted benzothiazoles can also be prepared from the corresponding trisubstituted aryl iodides with either electron-withdrawing and electron-donating groups as well as functional groups including bromo, amido, and ketone moieties. In certain cases, anhydrous potassium sulfide needed to be substituted for the sodium sulfide hydrate due to competing amide hydrolysis byproduct of labile amide groups (e.g., 2-furanyl). Aryl bromides also participate in the reaction in moderate to high yields (41−88%), although they require elevated temperatures (140 °C) and anhydrous potassium sulfide.

A Facile Route to Aryl Boronates: Room temperature, Copper-Catalyzed Borylation of Aryl Halides with Alkoxy Diboron Reagents

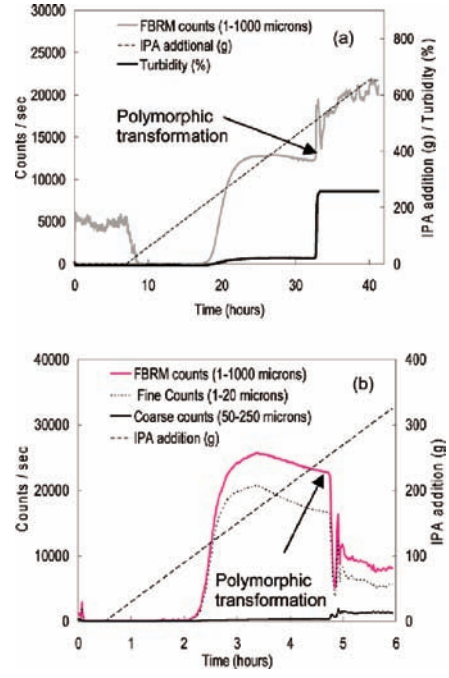


A cost-effective alternative to palladium-based borylation of aryl halides with alkoxy diboron reagents has been disclosed by Lin, Marder, and co-workers at Durham University in England (*Angew. Chem., Int. Ed.* **2009**, *48*, 5350−5354). Moderate to excellent yields of aryl boronates were obtained from a wide variety of their bromoaryl or iodoaryl counterparts under the standard conditions of CuI (10 mol %), nBuP$_3$ (13 mol %), a diboron reagent (B_2pin_2 or B_2neop_2, 1.5 equiv) and KO^{t}Bu (1.5 equiv) at room temperature in THF. This is a significant finding since at the time of the report, the only Cu(I) catalyzed borylation conditions utilizing CuI, NaH, and pinacolborane (see*Org. Lett.* **2006**, *8*, 261−263) were only are successful with aryl iodides, while aryl bromides proved not to be suitable substrates. Electron-rich and electron-poor substrates are tolerated as well as steric bulk, even in the *ortho* position. Unfortunately, aryl chlorides do not participate readily in the reaction. Limitations of the reaction are few but include functional group incompatibility with nitro groups, aldehydes, and ethers due to partial transetherification with KO^{t}Bu.

A Process Analytical Technology-Based Investigation of the Polymorphic Transformations during the Antisolvent Crystallization of Sodium Benzoate from IPA/Water Mixture

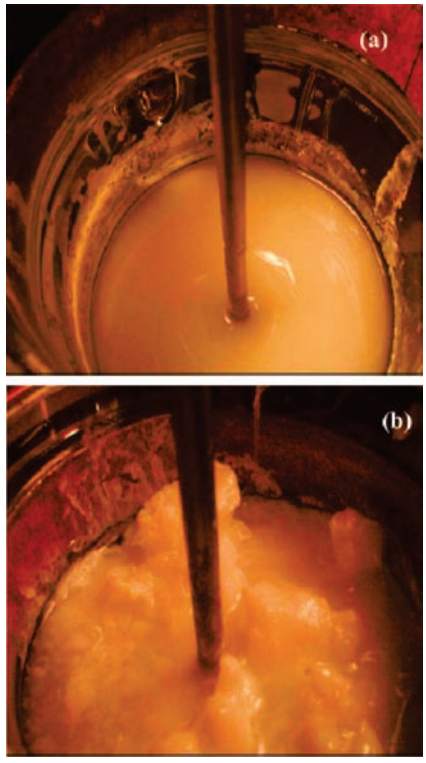
The results of crystallization investigations of well-known compounds using modern PAT methods continues to surprise. In a contribution from Loughborough University and Astra Zeneca (Howard, K. S.; et al. *Cryst. Growth Des.* **2009**, in press) the authors, among others, report the discovery of a new IPA solvate and a new, high-melting polymorph of sodium benzoate. The solvent system used was water/IPA, and the crystallization process was nonseeded, isothermal, using IPA as the antisolvent. The PAT tools employed were focused beam reflectance measurement (FBRM), ATR-UV spectroscopy, and turbidity monitoring. The challenge in defining the new solid-state forms is reflected by the very broad range of off-line solid-state analytical methods used: SEM, NMR (solid-, and solution-state), XRPD, and high-temperature XRPD, IR, TGA, DSC, optical microscopy, and hot-stage microscopy. The experiments were conducted in two different reactors, using different agitators, at different agitation speeds, and practicing different antisolvent addition times (0.33 g/min vs 1.0 g/min). The operational details are reported only in part, but it appears that the significantly different results obtained in the two reactors are a result of the different antisolvent addition rates used.

The following graphic shows FBRM and turbidity results for the antisolvent crystallization of sodium benzoate from an IPA/water mixture performed within a 1 L vessel using a (a) 3-blade glass retreat curve and (b) 4-pitched blade turbine (coated with PTFE).

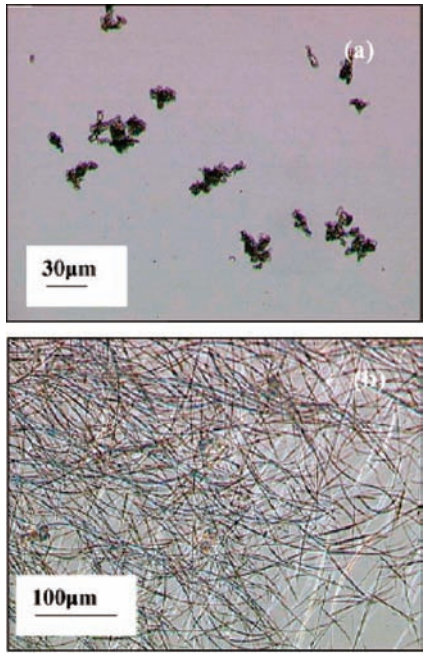


The graphics below refer to the experiments conducted using the 1.0 g/min IPA addition rate.

Visual images of the crystallization vessel showing (a) a mobile cloudy solution after the first nucleation event and (b) formation of solid clump after the second nucleation event.



Optical microscope images of the crystals obtained from the antisolvent crystallization experiments after (a) the first nucleation event and (b) the second nucleation event (fluctuation in FBRM counts).



Mixing and Dissolution Times for a Cowles Disk Agitator in Large-Scale Emulsion Preparation

Emulsion process scale-up continues to be challenging because of the complex interaction between the physicochemical properties of the system (often incompletely understood), including the interfacial characteristics, and the equipment performance. The flow behavior of such immiscible liquid−liquid systems is typically non-Newtonian, with limited process models available. Emulsion behavior, including phase inversion, can be system specific, complicating model development. Such scale-up problems are more difficult when the viscosities of the liquid streams being mixed are significantly different. The results of the investigation of such a problem were published by an industrial/academic team from Unilever and the University of Manchester (Rodgers, T. L.; et al. *Ind. Eng. Chem. Res.* **2009**, *48* (14), 6859.). Aqueous systems containing sodium lauryl sulfate (SLES) were investigated in a small ($D = 0.152$ m) and in a large reactor ($D = 0.914$ m); both reactors were fitted with single-stage high-shear agitators, albeit of different design: Cowles at large scale, and Torrance and Esco-Labor at small scale. The dissolution and mixing times were estimated using conductivity measurements. Observations made for different addition modes, and correlations for mixing times based on a modified Reynolds number are reported.

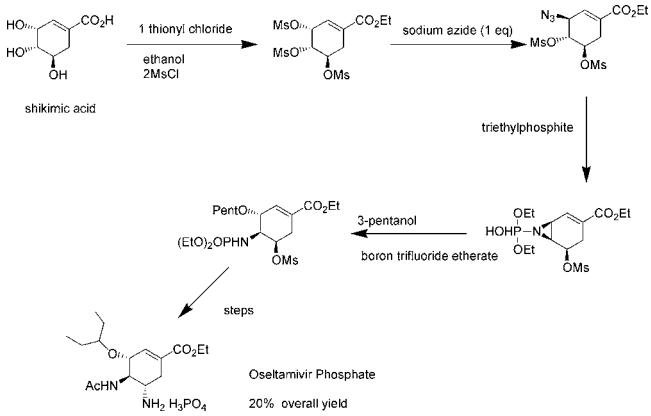
Rich Polymorphism in Triacetone Triperoxide

Triacetone triperoxide (TATP) is an interesting organic compound known since 1895, when one solid form was isolated. Unfortunately, TATP is also an improvised explosive used by terrorist organizations, for example in the July 7, 2005, attack in London. TATP is readily accessible from inexpensive supermarket items and cannot be easily detected using existing explosive-detecting methods. Because of this dubious notoriety, TATP re-entered research laboratories in order to be further understood. One of the groups who has dedicated a significant research effort in the area is Keinan's lab at the Israel Institute of Technology (Technion) in Israel. This group reported recently about several novel TATP polymorphs (Reany, O.; et al. *Cryst. Growth Des.* **2009**, *9*, 3661.). A typical TATP preparation uses equimolar amounts of acetone and hydrogen peroxide, in the presence of an acid catalyst. (∼1% v/v). When different acids were employed, it was found that in addition to the known polymorph, five more polymorphs were obtained. In certain cases, upon recrystallization from suitable solvents, pure polymorphs were produced, and single-crystal X-ray analysis was performed on all of the forms. It is noteworthy that polymorph control has been accomplished mostly using temperature, solvent, seeding, and crystallization additives, with fewer cases reported using pH to control the solid state of crystals. Interestingly, solid TATP decomposition is thermoneutral, but each TATP molecule produces four gaseous molecules: three acetone molecules and one ozone molecule.

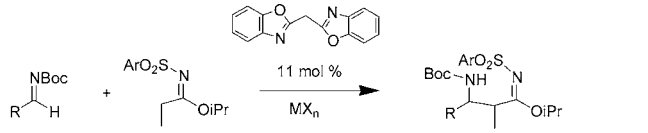
Efficient Synthesis of Oseltamivir Phosphate, the Active Ingredient of Tamiflu

This recent report (*Angew. Chem., Int. Ed.* **2009**, *48*, 5760−5762) from Roche process R&D describes a new and scalable synthesis of oseltamivir phosphate starting from shikimic acid. The paper debunks the myth, mentioned in several recent papers on Tamiflu synthesis, that shikimic acid is too expensive to use as a raw material and not readily available. In fact it is available from extraction of star anise and by fermentation. Hundreds of tons of low-cost material can now be made, and thus, it is the ideal starting material for the drug synthesis.

The new synthesis still uses azide chemistry, but the authors point out that the current manufacturing method, which also uses azide chemistry, has been used safely to make hundreds of tonnes of the drug. The new route is shown below. The key steps are the selective azide displacement in the trimesylate and its subsequent conversion to the phosphorylated aziridine, followed by ring-opening by pentanol. An overall yield of 20% can be obtained by this process, which has been patented.



Alkaline Earth Metals in Synthesis



Catalyst	Method	Yield	anti/syn
$Mg(O\ t\text{-}Bu)_2$	A	94	96:4
$Ca(O\text{-}iPr)_2$	B	68	11:89
$Sr(HMDS)_2$	B	92	7:93

method A: RT 17h, Ar = 2,5-xylyl
method B: RT 24h Ar = p-nitrophenyl

Calcium, magnesium, strontium, or barium catalysts are rarely used in organic synthesis, but this is changing. A recent article (*Angew. Chem., Int. Ed.* **2009**, *48*, 5790.) by Uli Kazmaier reviews recent work in the area. Owing to their low cost and abundance as well as low toxicity, these elements should be looked at more often in reactions by industry. The article discusses recent work on Michael, aldol, and Mannich reactions using alkaline earth catalysts, especially asymmetric versions, when high de and ee can be obtained. In the Mannich reaction, for example, *syn*/*anti* selectivity can be changed simply by changing from, say, a magnesium to a calcium, strontium, or barium catalyst and changing the aryl group on the sulphonylimidate catalyst.

Copper-Catalyzed Cross-Couplings with ppm Catalyst Loadings

This issue's editorial reminds us of the importance of trace metal contamination of metal catalysts. In another paper in the same issue of *Angew. Chem., Int. Ed.* (**2009**, *48*, 5691−3), the group of Carsten Bolm at Aachen have followed on the observation that copper contamination of iron catalysts may be responsible for their activity with a detailed study on the dependence of yield on the amount of copper(II) chloride applied in the reaction of iodobenzene with pyrrazole. They conclude that homeopathic amounts of copper can effect these Ullmann-type reactions. Best yields of 88% were obtained with catalyst at 0.01%. In other reactions good yields could be achieved with amounts as low as 0.001% of copper catalyst, but other reactions failed at this level; they could be achieved by adding more catalyst, however. It is not clear why these low levels of catalyst are successful in some cases. More work is needed to study mechanistic details or possible poisoning effects.

Mark McLaughlin

Merck & Co. Inc.,
Rahway, New Jersey 07065, U.S.A.
E-mail: mark_mclaughlin@merck.com

Matthew Pfeiffer

Process R&D, PTD, Exelixis Inc.,
South San Francisco, California 94080, U.S.A.
E-mail: mpfeiffe@exelixis.com

Andrei A. Zlota

The Zlota Company,
Sharon, Massachusetts 02067-2858, U.S.A.
E-mail: andrei.zlota@thezlotacompany.com

Trevor Laird*
Editor

OP900215M